

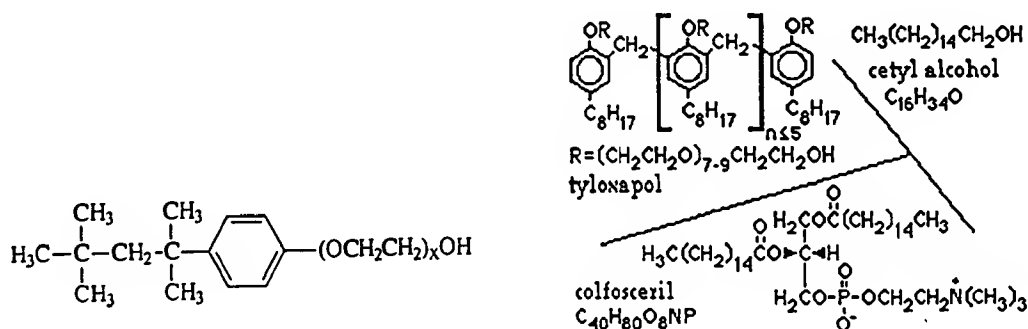
Examples of airway diseases that may be treated by the method of the present invention include cystic fibrosis, asthma, chronic obstructive pulmonary disease, bronchitis, and other airway diseases characterized by an inflammatory response. Antisense nucleotides to the A₁ and A₃ receptors are shown to be effective in the downregulation of A₁ or A₃ in the cell. One novel feature of this treatment, as compared to traditional treatments for adenosine-mediated bronchoconstriction, is that administration is direct to the lungs. Additionally, a receptor protein itself is reduced in amount, rather than merely interacting with a drug, and toxicity is reduced. Other proteins that may be targeted with antisense agents for the treatment of lung conditions include, but are not limited to: human A2a adenosine receptor, human A2b adenosine receptor, human IgE receptor β , human Fc-epsilon receptor CD23 antigen, human histidine decarboxylase, human beta tryptase, human tryptase-I, human prostaglandin D synthase, human cyclooxygenase-2, human eosinophil cationic protein, human eosinophil derived neurotoxin, human eosinophil peroxidase, human intercellular adhesion molecule-1 (ICAM-1), human vascular cell adhesion molecule-1 (VCAM-1), human endothelial leukocyte adhesion molecule-1 (ELAM-1), human P selectin, human endothelial monocyte activating factor, human IL-3, human IL-4, human IL-5, human IL-6, human IL-8, human monocyte-derived neutrophil chemotactic factor, human neutrophil elastase, human neutrophil oxidase factor, human cathepsin G, human defensin 1, human defensin 3, human macrophage inflammatory protein-1-alpha, human muscarinic acetylcholine receptor HM3, human fibronectin, human GM-CSF, human tumor necrosis factor α , human leukotriene C4 synthase, human major basic protein, and human endothelin 1. In these latter targets, and in target genes in general, it is particularly imperative to eliminate or reduce the adenosine content of the corresponding antisense oligonucleotide to prevent their breakdown products from liberating adenosine. --

Page 39, line 5 from the last, change "9941" into - 991) --.

Page 44, lines 6-7, delete "Brij 35, Triton X-100, and synthetic surfactants ALEC, Exosurf, Survan and Atovaquone", and substitute therefor -- polyoxy ethylene 23 lauryl ether (Brij 35[®]), t-octyl phenoxy polyethoxy ethanol (Triton X-100[®]), dipalmitoyl phosphatidyl choline (DPPC) and phosphatidyl glycerol (PG) (ALEC[®]), colfosceryl-cetyl alcohol-tyloxapol or colfosceril palmitate, cetyl alcohol and tyloxapol (Exosurf[®]),

phospholipids, neutral lipids, fatty acids and surfactant-associated proteins (Survanta[®]) and C₂₂H₁₉C₁₀ (Atovaquone[®]) --; and

after line 10, insert the following – The following chemical formulas are representative of the synthetic surfactants named below.



t-octyl phenoxy polyethoxy ethanol

Colfosceril-Cetyl Alcohol-Tyloxapol--.

Page 58, line 3 from the last, change "BUT" into –but--; and

before the last paragraph, insert the following:

Example 6: Additional Targets for Anti-sense Oligos in Accordance with the Invention

The method of the present invention is also practiced with the following antisense oligonucleotides targeted to their corresponding proteins, in essentially the same manner as given above, for the treatment of various conditions in the lungs:

Human A2a adenosine receptor: TGCTTTTCTT TTCTGGGCCT C (SEQ ID NO:997)

Human A2b adenosine receptor: GCGCCGTGC CGCTCTTGG TGGCGGCGG (SEQ ID NO:998)

Human IgE receptor β : TTTCCCTGG GTCTTCC (SEQ ID NO:999)

Human Fc-epsilon receptor CD23 antigen (IgE receptor): GCCTGTGTCT CTCCTCCT (SEQ ID NO:1000)

Human IgE receptor, " subunit: GCCTTCCTG GTTCTCTT (SEQ ID NO:1001)

Human IgE receptor, Fc epsilon R: GCCTGTGTCT GTCCTCCT (SEQ ID NO:1002)

Human histidine decarboxylase: TCTCCCTGG GCTCTGGCTC CTTCTC (SEQ ID NO:1003)

Human beta tryptase: CTTGCTCCTG GGGGCCTCCT G (SEQ ID NO:1004)

Human tryptase-I: CTTGCTCCTG GGGGCCTCCT G (SEQ ID NO:1005)

Human prostaglandin D synthase: GCGCTCGGCC TGGTCCCGG (SEQ ID NO:1006)

Human cyclooxygenase-2: GGGCGGGG GAGCATCGC (SEQ ID NO:1007)

Human eosinophil cationic protein: CCTCCTTCTT GGTCTGTCTG C (SEQ ID NO:1008)

Human eosinophil derived neurotoxin: GCCCTGCTGC TCTTCTGCT (SEQ ID NO:1009)

Human eosinophil peroxidase: GCGCTCGGCC TGGTCCCGG (SEQ ID NO:1010)

Human intercellular adhesion molecule-1 (CAM-1): GCGCGGGCCG GGGGCTGCTG GG (SEQ ID NO:1011)

Human vascular cell adhesion molecule 1 (VCAM-1): CCTCTTTCT GTTTTCCC (SEQ ID NO:1012)

Human endothelial leukocyte adhesion molecule (ELAM-1): GTTCTGGCT TCTTCTGTC (SEQ ID NO:1013)

NO:1013)

Human P Selectin: CTCTGCTGGT TTTCTGCCTT CTGCCC (SEQ ID NO:1014)

Human endothelial monocyte activating factor: TTTTCTCTTT CGCTTTCTTT TCGTCTCCTG TTCCTCCTTT T (SEQ ID NO:1015)

Human IL3: CTCTGTGTTG TTCTGGTCCT TCGTGGGGCT CTG (SEQ ID NO:1016)

Human IL4: CTCTGGTTGG CTTCCTTC (SEQ ID NO:1017)

Human IL5: TCCCTGTTC CCCCCTTT (SEQ ID NO:1018)

Human IL6: GCTTCTCTTT CGTCCCCGGT GGGCTCG (SEQ ID NO:1019)

Human monocyte-derived neutrophil chemotactic factor: GCTTGTGTGC TCTGCTGTCT CT (SEQ ID NO:1020)

Human neutrophil elastase (medullasin): TGGTGGGGCT GGGGCTCCGG GGTCTCTGCC CCTCCGTGC (SEQ ID NO:1021)

Human neutrophil oxidase factor: GTCCTTCTTG TCCGCTGCC (SEQ ID NO:1022)

Human cathepsin G: GTGGGGCCTG CTCTCCCGGC CTCCG (SEQ ID NO:1023)

Human defensin 1: GGGTCCTCAT GGCTGGGG (SEQ ID NO:1024)

Human defensin 3: GGGTCCTCAT GGCTGGGGTC (SEQ ID NO:1025)

Human macrophage inflammatory protein-1-alpha: GTCTTTGTTT CTGGGCTCGT GCC (SEQ ID NO:1026)

Human muscarinic acetylcholine receptor HM1: GTTCATGGTG GCTAGGTGGG GC (SEQ ID NO:1027)

Human muscarinic acetylcholine receptor HM3: GGGGTGGGTA GGCCGTGTCT GGGG (SEQ ID NO:1028)

Human fibronectin: CGGTTTCCTT TCGGGTC (SEQ ID NO:1029)

Human interleukin 8: GTGCTCCGGT GGCTTTTT (SEQ ID NO:1030)

Human GM-CSF: GGTCCAGCCA TGGGTCTGGG (SEQ ID NO:1031)

Human tumor necrosis factor ": GCTGGTCCTC TGCTGTCCTT GCTG (SEQ ID NO:1032)

Human leukotriene C4 synthase: GCCCCGTCTG CTGCTCCTCG TGCCG (SEQ ID NO:1033)

Human major basic protein: GTTTCATCTT GGCTTTATCC (SEQ ID NO:1034)

Human Targets 997-1034: GATGGAGGGC GGCATGGCGG GGTTGTTGGG CATCTTGCCG
 TGGGCCTAGC TCTCGCCTGC TTTCTTTTTC TGGGCCTCGG CGCCGTGCCG CGTCTTGGTG
 GCGGCGGTTT CCCCTGGGTC TTCCGCCTGT GTCTCTCCTC CTGCCTTTCC TGGTTCTCTT
 GCCTGTGTCT GTCCTCCTTC TCCCTTGGGC TCTGGCTCCT TCTCCTTGCT CCTGGGGGCC
 TCCTGCTTGC TCCTGGGGGC CTCCTGCGCT CGGCCTGGTC CCGGGGGCGC GGGCGAGCAT
 CGCCCTCCTT CTTGGTCTGT CTGCGCCCTG CTGCTCTTTC TGCTGCGCTC GGCTGTCTCC
 CGGGCGCGGG CCGGGGGCTG CTGGGCCTCT TTTCTGTTTT TCCCGTTCTT GGCTTCTTCT
 GTCCTCTGCT CGTTTTCTGC CTCTGCCT TTTCTCTTTC GCTTCTTTT CGTCTCCTGT
 TCCTCCTTTT CTCTGTGTTG TTCTGGTCCT TCGTGGGGCT CTGCTCTGGT TGGCTTCCTT
 CTCCCTGTTT CCCCCCTTG TTCTCTTC GTTCCCGGTG GGCTCGGCTT GTGTGCTCTG
 CTGTCTCTTG GTGGGGCTGG GGCTCCGGGTG TCTCTGCCCC TCCGTGCGTC CTCTTGTC
 GCTGCCGTGG GGCCTGCTCT CCCGGCCTCC GGGGTCTCA TGGCTGGGGG GGTCTCATG
 GCTGGGGTCG TCTTTGTTTC TGGGCTCGTG CCGTTCATGG TGGCTAGGTG GGGCGGGGTG
 GGTAGGCCGT TCTCGGTTTC CTTTGCGGTC GTGCTCCGGT GGCTTTTTTG TCCAGCCATG
 GGTCTGGGGC TGGTCTCTG CTGTCTTGC TGGCCCCGTC TGCTGCTCCT CGTGCCGGTT
 TCATCTTGGC TTTATCC (SEQ. ID NO:1035) --.

THE SEQUENCE LISTING

Please substitute the enclosed sequence listing section for the one filed November

15, 1999.